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TITLE: Efficacy of Calcium and Vitamin D Supplementation for the Prevention of Stress Fractures in Female Naval Recruits

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14. ABSTRACT: The goal is to determine if calcium and vitamin D supplementation can reduce the incidence of stress fracture by at least 50% in female Naval recruits during basic training. The secondary goal is to examine the potential mechanisms for increasing bone adaptation to intense mechanical loading. The Command Officers at the Great Lakes Naval Station stopped the study on xxx because we had recruited our originally targeted sample size. We recruited 5201 females who were randomly assigned to calcium 2000 mg and vitamin D 800 I.U. per day or a control placebo group. The intervention and stress fracture monitoring continued through 8 weeks of basic training. We were not able to recruit the targeted number of subjects for the sub-study designed to determine changes in moment of inertia using peripheral quantitative computed tomography(pQCT). We enrolled 148 (out of a target 560) In the 3703 participants who completed the main study we found that calcium/D supplementation decreased the incidence of stress fracture by 27%(p=0.02). Furthermore, supplementation suggest that supplementation can compensate for a history of low physical activity.					
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## INTRODUCTION

Stress fractures during military basic training remain a major concern despite training modifications that have decreased stress fracture incidence. Stress fractures are especially prominent in women. These injuries result in loss of manpower and high medical expense, occasionally incurring service-related disability. Supplementing female recruits with calcium and vitamin D may supply nutrients needed to meet training demands and thereby significantly reduce risk of fracture. Inadequate calcium and vitamin D intake may limit bone adaptation since recruits under 30 years of age have not achieved peak bone mass, training stimulates bone formation and micro-fracture repair, calcium intakes are normally low, and substantial dermal calcium losses occur during training. The goal of this project is to determine if calcium and vitamin D intervention can reduce the incidence of stress fracture by at least 50% in female Naval recruits during basic training. The secondary goal is to examine the potential mechanisms for increasing bone adaptation to intense mechanical loading.

## BODY

### Key Research Accomplishments

- Implementation of a project that does not interfere with the flow of Naval basic training
- Prompt restart of the project twice, including hiring and training of new study personnel
- Enrollment of 5201 subjects
- Completion of 3703 subjects
- Retention of 71% of enrolled subjects
- Implementation of pQCT sub-study
- Significant findings that calcium and vitamin D supplementation reduce the incidence of stress fracture by 27%.

Research accomplishments associated with each task outlined in the approved Statement of Work are outlined in Table 1.

<b>Table 1. Research Accomplishments Associated with Tasks in the Statement of Work</b>			
	Original	Actual/Projected	Explanation of discrepancies
Planning and set up	7/01-12/01	9/01-5/02	Although the project was funded 9/01, the DOD did not approve us to start until 4/02. We started one month after approval.
Enrollment, intervention and data collection	1/01 - 12/03	5/02 - 4/06	About 4.5 months after startup, enrollment was put on hold by the Great Lakes IRB for nearly 12 months (9/02-8/03). Great Lakes Command directed us to stop recruitment for another 8 months (1/05-8/05).
Data clean up and analysis; manuscript preparation	1/04-6/04	3/06 - 9/07	Delayed as described above

After receiving notification of funding, we worked with the DOD regulatory persons and the Creighton and Great Lakes Institutional Review Boards (IRB's) as quickly as possible to obtain approval for starting the study. We did not receive final approval from the DOD until April 2002. We started recruitment one month later. We were actively recruiting until September 26, 2002 when we were notified by the Great Lakes IRB that we were to stop recruitment and put the study on hold. We understand that all active clinical projects were stopped at the Great Lakes at that time. We were allowed to complete follow up of enrolled subjects.

The project was re-approved by the Great Lakes IRB and allowed to resume on August 7, 2003. We needed to hire new staff members since we had no funds to maintain our original staff during the shutdown

period. Within five weeks after re-approval we hired and trained new staff, and we resumed recruitment on September 18, 2003. Thus, we were delayed nearly a year with recruitment and data collection.

In September 2003, we were provided money from the DOD to purchase a Stratec peripheral quantitative computed tomography (pQCT) device. We submitted the protocol amendment for the pQCT measurements to the Great Lakes IRB in September 2003 and received approval in January 2004. We immediately requested that the DOD approve the protocol amendment, but we did not receive that approval until June 2004. We then hired and trained a person to do the pQCT measurements and started the pQCT sub-study in July, 2004. We completed the pQCT precision study, and then in October 2004 the pQCT started to malfunction. The first year warranty that was included in the purchase price expired while we were waiting for approval to start the pQCT study. The repair estimate was \$10,000. We asked for extra funds from the DOD to repair the pQCT in November 2004. In the meantime, we selected a contractor, obtained a repair quote and put in a purchase order with the university so that we could have the pQCT repaired. In January 2005, the Great Lakes Command directed that we stop all recruitment until we were able to use the pQCT.

We had the device repaired and hired and trained a new technician since our first one had taken another job. We also did a small precision study to assure that the repaired device had reliability. We were ready to restart in June 2005, but the Recruit Training Command at the Great Lakes asked us to wait until August 2005 to restart the study, which we did.

In March 2006, the Command Officers at the Great Lakes ordered us to stop the study because we had reached our target sample size for the main study (5200). We enrolled 5201 subjects in the main study but only 148 in the pQCT sub-study (target sample size – 560). Of those enrolled, 362 were discharged from the Navy before the end of training and an additional 1136 withdrew from the study. Our retention rate was 71%.

The mean age of the study participants is 20.2 ( $\pm 2.7$ ) years. The ethnic/racial breakdown is as follows: American Indian/Alaskan 3.41%; Asian 4.16%; Black/non-Hispanic 17.94%; Hispanic or Latino 12.66%; White/non-Hispanic 58.87% and other 2.95%. 285 of the study subjects sustained a stress fracture. Stress fractures were confirmed by either radiograph or technetium bone scan.

Table 2 shows descriptive characteristics of the sample.

<b>Table 2. Description of Sample</b>		
Variable	N	Median (range)
Dairy servings/wk	5025	6 (1-26)
Alcohol drinks/wk	1621	3 (1-12+)
Cigarette packyears	985	3 (1-24)
Birth control pills (yrs use)	2266	2 (1-18)
Depomedroxyprogesterone	827	1 (1-13)
Progesterone implant	37	1 (1-10)

Fisher's Exact analysis found that the calcium/vitamin D group had a 27% lower incidence of stress fractures than the control group (6.8% vs 8.6% respectively,  $p=0.02$ ). (See Figure.) In the placebo group, those who reported a history of weight-bearing physical activity at least three times every week or most weeks had a significantly lower risk of stress fracture than those who reported less activity (RR 0.6,  $p=0.003$ ). This effect was not seen in the treatment group.

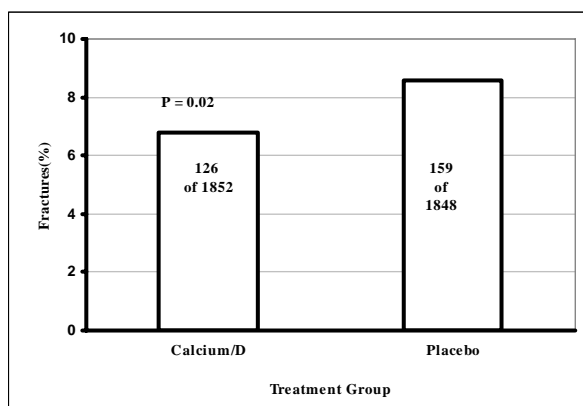


Figure 1. Percent of recruits with incident stress fracture in the calcium/vitamin D group compared to the placebo group.

We are continuing data analysis and are preparing a paper for submission early in 2007.

### Reportable Outcomes

We have made four presentations on this study, and we have an abstract accepted for an oral presentation :

Lappe, J., Cullen, D., Thompson, K., Ahlf, R. (2006) Calcium and vitamin D Supplementation Reduces Incidence of Stress Fractures in Female Navy Recruits. Selected for oral presentation at the Annual Meeting of the Orthopedic Research Society, San Diego CA, Feb 11<sup>th</sup>.

Lappe, J., Cullen, D., Thompson, K.(2006) Calcium and vitamin D Supplementation Reduces Incidence of Stress Fractures in Female Navy Recruits. Presented to the Command Officers of the Great Lakes Naval Station, June 15<sup>th</sup>.

Ahlfs, R., Lappe, J., Cullen, D., Thompson, K. (2005) Efficacy of calcium and vitamin D supplementation for the prevention of stress fractures in female Naval recruits. Oral presentation at the Accessions Research & Best Practices Symposium, August 23-25, Lincolnshire IL.

Lappe, J., Cullen, D., Thompson, K.(2004) An update on the study of calcium and vitamin D to prevent stress fractures. Oral presentation to the GlaxoSmithKline Calcium Board. Seattle, September 28.

Lappe, J. (2004) Efficacy of calcium and vitamin D supplementation for the prevention of stress fractures in female naval recruits. Oral presentation. U.S. Army Accessions Command, Accessions Research Consortium, Fort Jackson S.C.

### Conclusions

Calcium and vitamin D supplementation significantly reduces the incidence of stress fractures in female Navy recruits during basic training. The findings suggest that supplementation can compensate for a history of low physical activity.

### References

None

### Appendices

None